EXHIBIT B

CV

**SCHERING-PLOUGH CORPORATION**

**RECORD OF INVENTION**

DISCLOSURE NO. 3669

**IMPORTANT:**

1. Fill out this form completely. If no experiments or tests have been performed, please indicate.
2. Supplement this record with a complete description of the invention including drawings, if possible, discussion of utility, variations, important features and advantages. Where the invention is a chemical compound, the process (or processes) for preparing the inventive compounds disclosed must be shown. This process must start from known compounds. Please indicate references for recently published compounds.
3. Please remember that every page of this record must be signed by the suggested inventor or all the suggested inventors and witnessed, the signature of each suggested inventor and witness must be dated, and the original sent immediately to the Patent Department. The suggested inventor(s) must cross out the remaining blank portion of each page and sign each page where indicated.

SUBJECT MATTER: The use of azetidinone compounds (ezetimibe, SCH58235) to inhibit the intestinal absorption of plant sterols.

SUGGESTED INVENTOR(S): Harry R. Davis, Jr.

FIRST DISCLOSED TO Glen Tetzloff DATE

FIRST DRAWING OR WRITTEN DESCRIPTION DATE

FIRST EXPERIMENTS AND/OR TESTS DATE

**One of the following boxes (A - F) MUST be checked.**

This invention was:

- [X] A. not derived from DNA sequence information
- [ ] B. derived from DNA sequence information obtained from public or SP databases
- [ ] C. derived from DNA sequence information obtained from Incyte databases
- [ ] D. derived from DNA sequence information obtained from the HGS database
- [ ] E. derived from DNA sequence information obtained from the GTC/ PathoGenome™ database
- [ ] F. derived from DNA sequence information obtained from other source: please specify

If Box B, C, D, E or F is checked, indicate **Notebook Number and Page Reference** to document data base source:

Notebook Number: 39040 Page Number(s): 64-75 Date:

**Notebook Documentation ascertained by:**

| Name | Signature | Date |
|---|---|---|
| Arthur Brown | Arthur Brown | |

**Notebook Documentation reviewed and approved by (Senior Director or above):**

| Name | Signature | Date |
|---|---|---|
| John C. Hunter | | |

WITNESSED AND UNDERSTOOD BY:

| | Signature | Date |
|---|---|---|
| Doug Compton, WITNESS (NON INVENTOR) | | |
| Lizbeth Hoos, WITNESS (NON INVENTOR) | Lizbeth Hoos | |
| Catherine Strader, Approved by: VICE PRESIDENT | | |
| ANITA MARKATT, Acknowledged by: PATENT DEPT. | | |

SUGGESTED INVENTORS

| Name | Signature | Date |
|---|---|---|
| Harry R. Davis, Jr. | | |
| | | |
| | | |

**SCHERING-PLOUGH CORPORATION** **RECORD OF INVENTION**



BRIEF DESCRIPTION INCLUDING UTILITY OF THE INVENTION (WITH SKETCH IF APPROPRIATE). TRY TO GIVE BOTH BROAD SCOPE AND PREFERRED EMBODIMENTS. INCLUDE "SCH" NUMBERS IF AVAILABLE.

The use of azetidinone compounds (ezetimibe, SCH58235) to inhibit the absorption of plant sterols.

Azetidinone compounds, like ezetimibe (SCH58235) have been found to be potent cholesterol absorption inhibitors, which reduce plasma cholesterol levels and inhibit atherosclerosis. Cholesterol absorption studies with SCH58235 in mice using a fecal isotope ratio method revealed an unexpected finding that SCH58235 inhibited the absorption of the plant sterol sitosterol. Tritiated sitosterol was used an "unabsorbable" marker to compare to the absorption of [14C]-cholesterol in a mouse fecal isotope ratio cholesterol absorption model. Wild type mice (C57BL/6J) and mice deficient in apoprotein E (Apo E KO) were found to absorb from 0.15-0.38% of the [3H]-sitosterol dose into their livers and SCH58235 was found to dose dependently inhibit the absorption and hepatic accumulation of sitosterol (Table 1).

Sitosterolemia is a genetic disorder, which is characterized by increased plasma levels of sitosterol and other plant sterols, due to an increased nonselective intestinal absorption of sterols. Individuals with sitosterolemia have accelerated atherosclerosis, myocardial infarctions, and die at an early age due to extensive coronary atherosclerosis. Drug treatment for sitosterolemia is primarily with bile acid sequesterants (cholestyramine), but compliance is difficult due to constipation. The HMG CoA reductase inhibitors have failed to reduce plasma cholesterol or sitosterol levels in homozygote sitosterolemics. Current treatments also include ileal bypass surgery and selective low density lipoprotein plasmapheresis. Ezetimibe (SCH58235) may be useful in the treatment of sitosterolemia, by inhibiting the absorption of cholesterol and plant sterols like sitosterol.

WITNESSED AND UNDERSTOOD BY:

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| Doug Compton<br>WITNESS (NON INVENTOR) | Signature | Date |
| Lizbeth Hoos<br>WITNESS (NON INVENTOR) | Signature | Date |
| Catherine Strader<br>Approved by: VICE PRESIDENT | Signature | Date |
| Anita Mahanty<br>Acknowledged by: PATENT DEPT. | Signature | Date |

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| Harry R. Davis, Jr.<br>Name | Signature | Date |
| Name | Signature | Date |
| Name | Signature | Date |

**SCHERING-PLOUGH CORPORATION** **RECORD OF INVENTION**



Table 1.

Effect of SCH 58235 on Sitosterol Absorption in Mice

| Mouse strain | Treatment | Liver Sitosterol, % of administered Dose average ±sem | p = |
|---|---|---|---|
| C57BL/6J | Vehicle Control | 0.1479 ±0.0337 | |
| | SCH 58235-0.3mg/kg | 0.1093 ±0.0143 | |
| | SCH 58235-1mg/kg | 0.0588 ±0.0115 | 0.046 |
| | SCH 58235-3mg/kg | 0.0489 ±0.0067 | 0.024 |
| | SCH 58235-10mg/kg | 0.0552 ±0.0151 | 0.040 |
| ApoE KO | Vehicle Control | 0.3773 ±0.0525 | |
| | SCH 58235-0.3mg/kg | 0.1863 ±0.0246 | 0.013 |
| | SCH 58235-1mg/kg | 0.1019 ±0.0225 | 0.0019 |
| | SCH 58235-3mg/kg | 0.0772 ±0.0050 | 0.0023 |
| | SCH 58235-10mg/kg | 0.0780 ±0.0179 | 0.0017 |

Data found in NB 39040, p.64-75
N = 4-6 mice per treatment

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